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Hypercholesterolemia and cardiovascular disease: Focus on high cardiovascular risk patients

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A B S T R A C T

The widespread use of statins has largely improved the treatment of hypercholesterolemia, but many patients still fail to achieve the LDL-C targets recommended by guidelines. Furthermore, some patients continue to present a very high cardiovascular (CV) risk or even an extreme risk despite being well treated, mainly due to the presence of co-morbidities such as diabetes or peripheral artery disease, which significantly increase their global CV risk. For these very high CV risk patients, the most recent European guidelines have reviewed the LDL-C goals and recommend an LDL-C reduction of at least 50% and a goal of <55 mg/dL or even <40 mg/dL. Recent clinical trials have shown that patient stratification based on the presence or absence of atherothrombotic risk factors may represent a valuable tool to identify patients at extremely high CV risk who may benefit more from an aggressive LDL-C-lowering approach. In these patients it may be appropriate to aim for the lowest LDL-C level, independently of recommended goals, with all the available pharmacological approaches.

1. Introduction

Despite the substantial improvement in the treatment of hypercholesterolemia, essentially due to the widespread use of statins, many patients still fail to achieve the LDL-C targets recommended by guidelines, thus resulting in a loss of clinical benefit [1,2]. Among patients at very high cardiovascular (CV) risk [3], some categories may be considered at extreme risk and include patients with recurrent acute coronary syndrome (ACS) despite LDL-C levels <70 mg/dL, patients with CV disease (CVD) and diabetes, advanced chronic kidney disease (CKD) or familial hypercholesterolemia (FH). For such patients the most recent European guidelines have reviewed the LDL-C goals and recommend an LDL-C reduction of at least 50% and a goal of <55 mg/dL or even <40 mg/dL [3], in agreement with AACE/ACE guideline indications [4].

Here we discuss the evidence of the clinical effects of further reducing LDL-C levels in these very high risk patients.

2. Patients at very high CV risk

Among patients with stable coronary artery disease (CAD), a high proportion presents an extreme CV risk, due to the presence of specific risk factors, including diabetes mellitus or FH [5]. Despite being on lipid-lowering treatment, only a small percentage achieves LDL-C<70 mg/dL (20.3%) or <55 mg/dL (5.3%) [5]. This results from the inappropriateness of the therapy, as most of them (~77%) were on statin monotherapy [5,6]. This represents a substantial therapeutic gap, that could be tackled by using high intensity statin therapy, even in combination with ezetimibe and PCSK9 inhibitors when required [3], with the aim to obtain substantial reductions of LDL-C levels. The clinical benefit related to additional reductions of LDL-C levels has been proven by the IMPROVE-IT trial, which recruited patients within the first 10 days after an ACS, treated with simvastatin + ezetimibe or simvastatin monotherapy. After a

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median follow-up of 6 years, the addition of ezetimibe to simvastatin lowered LDL-C by ~24%, which translated into a significant 2% absolute risk reduction in the primary composite endpoint of CV death, major coronary events or nonfatal stroke [7]. Although this result is overall suggestive of a clinical benefit of adding ezetimibe to simvastatin in post-ACS patients, risk stratification based on the presence of specific atherothrombotic risk indicators (including congestive heart failure, hypertension, diabetes mellitus, age≥75, prior stroke, prior CABG, peripheral artery disease, moderate-to-severe CKD, smoking) allows the identification of higher risk patients who would experience the greatest absolute benefit from this combination therapy [8]. Thus, when this 9-point risk stratification tool is applied to the IMPROVE-IT population, the cumulative incidence of CV death, myocardial infarction (MI) or ischemic stroke during a follow-up period of 7 years increases from 8.6% with none of these indicators up to 68% in the presence of ≥5 indicators [8]. Using this tool, patients enrolled in the IMPROVE-IT study were divided into a low risk category (0–1 risk indicators), intermediate-risk (2 risk indicators) and high risk (≥3 risk indicators); as expected, the cumulative incidence of CV events significantly increased across these categories [8]. The extent of CV risk reduction observed when ezetimibe was added to simvastatin was strictly dependent on the risk category: low-risk patients showed no risk reduction, patients at intermediate risk showed a 11% relative risk reduction (−2.2% absolute risk) and high risk patients had a 19% relative risk reduction (−6.3% absolute risk) [8].

When this risk score, integrated with the presence of prior MI as additional indicator, was applied to the population of the FOURIER trial on evolocumab, intermediate-risk patients (79% of the whole population) showed a 1.9% absolute risk reduction in CV death, MI or stroke at 3 years with evolocumab compared to placebo; a greater benefit was obtained in highest-risk patients (16% of the population) who showed a 3.6% absolute risk reduction [9]. These findings have been received by the recent European guidelines, which now recognize that some patients need a more aggressive approach with lower cut-off levels and suggest to consider PCSK9 inhibitors in these patients on a best available statin therapy with ezetimibe [3,10].

Similar results were obtained when the population of the FOURIER trial was stratified according to the presence of diabetes at baseline, the number of previous MI or the presence of multivessel disease (Table 1); in the placebo arm, the risk was higher if patients had an MI within the first 2 years, or had ≥2 MI compared with just an episode of MI prior the enrolment, or in the presence of multivessel disease [11]. We must acknowledge that the placebo arm in this trial was in high intensity (70%) or moderate statin treatment (25–30%), with baseline LDL-C ~90 mg/dL [11]. The two subgroups (≥2 MI or multivessel disease) in the placebo arm identify patients that, despite treated with high intensity statin regimen, remain at remarkable risk for events [11]. In patients with ≥2 prior MI the addition of evolocumab leads to a remarkable reduction in LDL-C levels (~60%), translating into a 3.7% absolute risk reduction for the primary endpoint and 18% relative risk reduction; in patients with only 1 prior MI, the decrease in absolute risk was 1.3% (8% relative risk reduction) [11]. Thus, although patients with the greatest burden of coronary atherosclerosis had the greatest clinical benefit from aggressive LDL-C lowering, they were still at higher risk compared with the subgroups of patients with 1 prior MI or no multivessel disease on placebo, and despite their very low LDL-C levels [11]. Another major point arisen from the FOURIER trial is the relevance of peripheral artery disease (PAD) in increasing the CV risk: the stratification of patients based on the presence of PAD (which greatly increases the CV risk) shows that the clinical benefit of adding evolocumab to their current therapy is greater in patients with PAD [12]. Similar results were obtained when patients were stratified according to the presence of diabetes at baseline [13]. Altogether these observations indicate that patient stratification based on the presence or absence of atherothrombotic risk factors may represent a valuable tool in clinical practice to identify patients at extremely high cardiovascular risk who may have the greatest benefit from an aggressive LDL-C-lowering. In these patients it may be appropriate to aim for the lowest LDL-C level, independently of recommended goals, with all the available pharmacological approaches (Fig. 1). We must acknowledge, however, that many patients with very low LDL-C levels may still present a residual CV risk due to the presence of independent risk factors (such as inflammation or high levels of Lp(a)).

Table 1
Evolocumab-induced risk reduction in patients stratified according to the presence of specific pathological conditions.

Underlying condition	RRR	ARR	NNT
Diabetes at baseline [13]			
Yes	17%	2.7%	37
No	13%	1.6%	62
Number of prior MIs [11]			
≥2	21%	2.6%	38
1	16%	1.7%	60
Multivessel disease [11]			
Yes	30%	3.4%	29
No	11%	1.3%	78
Presence of PAD [12]			
Yes	27%	3.5%	29
No	19%	1.4%	72

MI: myocardial infarction; PAD: peripheral artery disease; RRR: relative risk reduction; ARR: absolute risk reduction; NNT: number needed to treat.

3. Familial hypercholesterolemia

Familial hypercholesterolaemia is a genetic disorder affecting the hepatic clearance of LDL particles, resulting in a marked elevation of plasma LDL-C and early atherosclerosis [14]. FH is a unique amplifying risk factor for premature coronary disease; in fact, compared with the background population, a subject with heterozygous FH reaches the LDL-C burden sufficient to develop coronary heart disease 20 years earlier (if untreated), and for a homozygous FH this occurs during adolescence [14]. However, despite the clinical relevance of FH and its high prevalence in the general population, there are several gaps in detection and care [14]. FH is in fact a common disorder, with an estimated prevalence of 1 in 200/300 in the general population (for the heterozygous form), and therefore it can be viewed as a public health issue; this prevalence is, as expected, even higher among patients with acute coronary disease (about 1 in 21), and this represents a great opportunity to detect the disorder [15].

Several detection strategies exist, including universal screening, systematic screening (such as cascade testing) and opportunistic screening (in coronary care units or primary care). Cascade testing for FH is an evidence-based detection method: it leads to early detection and initiation of preventive therapy, a better adherence to therapy and attainment of LDL-C goals, it reduces coronary events, it is proven to be cost effective and it proves reassurance for relatives who screen negative. Cascade screening starts with the identification of an index case, and proceeds with the DNA testing in family members at any age [16]. Some difficulties may present, however, with cascade testing, including lack of skills among providers, poor communication within families and family dynamics, as well as issues with privacy policy and healthcare systems [17–21]. Universal screening of children may represent a relevant clinical tool, as it gives the opportunity for early interventions (both lifestyle and therapeutic), significantly reducing cumulative LDL-C

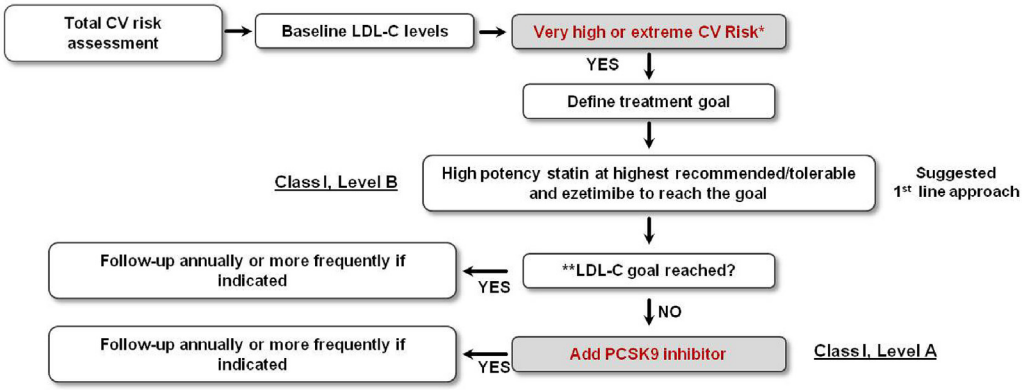

Fig. 1. Model of therapeutic approach in patients at high and extreme cardiovascular risk.
*Extreme CV Risk: diabetes and CHD, multivessel CV disease, PAD, recurrent MI, HeFH and CHD, HeFH with other CVD risk factors; ** LDL-C assessed after 4–6 weeks.
CV: cardiovascular; HeFH: Heterozygous familial hypercholesterolemia, LDL-C: low density lipoprotein cholesterol; PCSK9: proprotein convertase subtilisin/kexin type 9 Adapted from: Mach F et al. Eur Heart J 2020; 41(1):111–188.

burden and their CV risk in adulthood [22,23]. This approach may be integrated with a reverse cascade screening, by testing the parents and then, eventually, the rest of the family [24,25], thus allowing to identify FH patients before the occurrence of a clinical event.

Diagnosis and genetic testing. The most widely recommended approach for the clinical diagnosis of FH is the application of the Dutch Lipid Clinic Network (DLCN) score, based on data on family history, clinical history, presence of specific physical signs, LDL-C levels, and DNA testing [14]. Despite being costly, genetic testing in FH increases considerably the precision of the diagnosis, improves risk prediction, facilitates cascade screening, improves the use of genetic counseling, enables good therapeutic choices and improves adherence to therapy [26–28].

Treatment and targets. The new ESC/EAS guidelines for the management of dyslipidemias have introduced new/upgraded recommendations for the treatment of patients with FH. As first, individuals with FH and ASCVD or another major risk factor are classified as very-high risk patients, for whom an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered, and if the goal cannot be achieved, a drug combination is recommended [3]; patients with FH without other major risk factors are high risk patients and for them an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) are recommended [3]. Treatment with a PCSK9 inhibitor is now recommended in very-high-risk FH patients when the treatment goal is not achieved on maximally tolerated statin plus ezetimibe. Treatment options for FH should consider four principles: earlier, lower, longer and safer, and must include the adoption of a healthy lifestyles, therapies with established drugs (statins, ezetimibe, resin, niacin) commonly combined with more recent lipid-lowering agents (apoB antisense, PCSK9 inhibitors, MTP inhibitors) [3], or advanced and radical therapies such as lipoprotein apheresis (that has a major role in the management of homozygous FH) and liver transplantation for the most severe homozygous cases. Although monoclonal antibodies (mAbs) against PCSK9 effectively reduce LDL-C levels in HeFH patients [29–31], we must acknowledge that in HoFH PCSK9 mAbs are effective only in patients carrying LDLR defective mutations, who have a residual LDLR expression, whereas patients with null mutations do not respond to this therapy [32]. This implies that knowing the causative mutation in HoFH helps in the choice of the appropriate therapy, which represents a relevant issues, since the risk of death from any cause and from cardiovascular events are strictly related to the on-treatment plasma cholesterol levels [33]. New approaches for the management of HoFH include evinacumab, a monoclonal antibody targeting ANGPTL3, that has been shown to halve LDL-C levels in HoFH patients independently of LDLR [34].

4. High CV risk patients: adherence and persistence to therapy

Although many recent trials have shown that aggressive lipid lowering therapies with combination of drugs significantly reduce both LDL-C and atherosclerotic burden in very high risk patients [35,36], a major concern in CV prevention is the adherence and persistence of these patients to therapy in the daily practice. In fact, an early discontinuation of therapy translates into an increased cumulative incidence of cardiovascular events and death compared with prolonged use of lipid-lowering drugs [37].

In clinical practice, cholesterol-lowering drugs, particularly statins, are associated with a poor adherence (ranging from 30% to 60% within 1 year after therapy initiation), despite the persistence of treatment over time according to guideline-recommendations always associated with improved clinical outcomes [38]. Several factors are associated with non-adherence to therapy, which may be classified into three categories: patient-related factors (either voluntary or involuntary), physician-related factors (including poor awareness about patient adherence, multiple physicians providing advice), and health care system-related factors [39]. A major issue related with statin therapy is the occurrence of statin-associated muscle symptoms, but the notion of the “nocebo effect” has challenged this causal association [40], at least for most muscle adverse events reported during statin treatment. Specific interventions, aimed at increasing the knowledge of a long-term statin benefit may result in an improved medication adherence, which in turn will reduce morbidity and increase life expectancy [39].

5. Conclusion

Some categories of patients present a very high cardiovascular risk; the availability of established LDL-C-lowering drugs and the most recent pharmacological approaches allows an effective reduction of plasma cholesterol levels when used in combination. This represents the best approach to manage patients with extreme CV risk, in whom it may be appropriate to aim for the lowest LDL-C achievable, and who may benefit more from an aggressive approach compared with patients at a lower CV risk.

CRediT authorship contribution statement

Gerald F. Watts: Supervision. **Alberico L. Catapano:** Conceptualization, Supervision. **Luis Masana:** Supervision. **Alberto Zambon:** Supervision. **Angela Pirillo:** Writing - review & editing. **Lale Tokgözoğlu:** Supervision.

Declaration of competing interest

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